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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/036,869 | 11/29/2001 | A. James Mixson | 38147-0017 | 9568 |

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| EXAMINER | |
|---|---|
| SCHNIZER, RICHARD A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 01/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/036,869 | MIXSON, A. JAMES | |
| | Examiner | Art Unit | |
| | Richard Schnizer, Ph. D | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21-35 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-35 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

An amendment was received and entered on 10/21/04.

Claims 36-40 were canceled, and claim 41 was added as requested.

Claims 21-35 and 41 are pending and under consideration in this Office Action.

### *Rejections Withdrawn*

The rejection of claims 21, 23-26, 28-36, and 38-40 for failing to enable the full scope of the claims is withdrawn. Applicant argues essentially that one of skill in the art would know when subcutaneous administration is effective, and when it is not. For example it would be effective in the context of administration into a site adjacent to a tumor, wherein the site provides blood supply to the tumor. The argument is persuasive.

### *Priority*

This case is a continuation of 09/500,838, which is a continuation in part of 08/985,526, now abandoned, which is a continuation in part of 08/680,845, filed 12/5/97, now issued as US Patent 6,080,728. Instant claims 21-35 and 41 are drawn to methods of inhibiting tumor growth through administration of a nucleotide sequence in a in a carrier that is either liposomes, cationic polymers, micelles. The term "nucleotide sequence" is interpreted by the Examiner to include RNAs. As such, the claims continue to embrace methods of inhibiting tumor growth through administration of RNA. As noted previously, 08/985,526 provides no support for this embodiment, and the

'728 patent provides no support for delivering RNA by liposomes, cationic polymers, micelles, or combinations of these carriers. For these reasons, to the extent that the claims read on methods of delivering RNA, the priority date for the claims is considered to be 2/10/00, the filing date of 09/500,838.

***Response to Arguments***

Applicant's arguments filed 10/21/04 have been fully considered but they are not persuasive. Applicant argues at page 4 of the response that the term "nucleotide sequences" is fully supported by the '526 parent application. For evidence Applicant points for to column 9, line 4 of the parent patent (US 6,080,728). Applicant's argument is unpersuasive because this passage refers to DNA sequences, as is made clear when it is reproduced in the context of the specification from column 7, line 37 through the passage in question. Column 7, lines 37-39 state: "The particular anti-angiogenic protein or peptide encoded by the anti-angiogenic DNA is not critical to the present invention. Examples of suitable peptides include:". This passage is followed by a list of 16 DNA sequences from column 7, line 40 to column 8, line 33. The next paragraphs at column 8, lines 34-56 indicate that invention is not limited to these precise DNA sequences, noting that the DNA sequences can be used in concatemeric form. Column 8, line 57-65 to column 9, line 7 are reproduced below.

> Since more than one anti-angiogenic pathway exists, concatamers consisting of two or more types of inhibitor could be more effective than homogenous concatamers. For example, heterogeneous concatamers of TSPI and the fibronectin inhibitors can be inserted into the same vector. An example of such a heterogenous concatamer encoding DNA is shown in SEQUENCE ID NO: 31. In such heterogenous concatamers, the peptide-encoding repeats of each sequence may be linked in blocks and/or randomly.
>
> The heterogeneous concatamers need not be limited to only anti-angiogenic peptides. For example, the protein angiostatin or the large polypeptide fragment of prolactin can be modified with genes encoding anti-angiogenic peptides. Again, the concatameric number will vary

depending on the number of **nucleotide** bases of the unit angiogenic inhibitor. In a concatamer of large and small anti-angiogenic inhibitors, the ratio of large to small inhibitors is 0.1 to 0.9, preferably 1:1.

The instance of the term "nucleotide" relied upon by Applicant to support the disclosure of RNA is shown above in bold. IN the specification of '728, this term is used to describe the length of a concatemeric sequence encoding one or more angiogenesis inhibitors. It is clear from the '728 specification as a whole, particularly from column 7, line 37 to column 9, line 7, that the term "nucleotide" at column 9, line 4 was used to describe a DNA nucleotide, because this passage of the specification is directed to a discussion of DNAs, not RNAs or nucleic acids broadly. As such, there is no support for broadening the interpretation of "nucleotide" in this context to include RNA. In contrast, it is clear that the term "nucleotide" in the instant specification embraces RNA. See the instant specification at page 19, lines 4-6. So, the claims continue to embrace RNA, and to the extent that they do, they lack support in the '526 parent application and the '728 patent. To the extent that the instant claims embrace RNA, their effective filing date is 2/10/00, the filing date of 09/500,838.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321□ may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21-35 and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 16, and 17 of U.S. Patent No. 6,080,728 ('728). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Instant claims 21-25, 32, 33, and 41 are methods of inhibiting tumor growth in a subject bearing a tumor by administering in a carrier a nucleic acid that inhibits tumor angiogenesis, wherein the carrier is selected from the group consisting of liposomes, cationic polymers, micelles, and a combination thereof. Instant claims 26-31, 34, and 35 are more broadly drawn to methods of providing anti-angiogenic therapy using the same method steps as those in claims 21-25, 32, 33, or 41. Instant claims 22 and 37 require intravenous injection. Instant claims 23-25 and 29-31 limit the nature of the carrier to species recited in independent claims 21 and 26.

Claim 1 of '728 is drawn to a method of inhibiting tumor growth by administering to a subject a DNA encoding an anti-angiogenic protein with a carrier which may be a liposome, a micelle, or a cationic polymer. Claim 2 requires intravenous injection, and claims 3-5 require a liposomal carrier, a cationic polymer carrier, or a micelle carrier, respectively. These claims anticipate, and render obvious, instant claims 21-27 and 29-31.

Instant claims 28 and 41, require injection into a tumor. These claims are obvious because claim 1 of '728 is broadly drawn to "inhibiting tumor growth by administering to a subject a DNA encoding an anti-angiogenic protein", and clearly embraces intratumoral injection. One of ordinary skill in the art wishing to understand the intended breadth of the claim term "administering" would refer to the specification, e.g. at detailed description paragraph 46 which states:

> The particular mode of administering the carrier:DNA complex of the present invention depends on various factors, but preferred modes include intravenous, subcutaneous or **intratumoral injection**. Intravenous injection is the preferred administration mode for distribution of the complex to the developing blood vessels of the tumor.

Emphasis added. Thus claim 1 clearly embraces intratumoral injection.

Instant claims 32-35 require administering a nucleic acid encoding a tumor suppressor such as p53. These claims are obvious over claims 16 and 17of '728, which require "injection of DNA encoding at least one anti-angiogenic protein or peptide and DNA encoding a tumor suppressor protein". Claim 17 requires that the tumor suppressor protein is p53

At page 4 of the response, Applicant requests that the rejection be held in abeyance until the claims are in condition for allowance, "as is permitted in the M.P.E.P." The Examiner is unaware of any provision for holding a rejection in abeyance, and Applicant has failed to point to any. The rejection is not held in abeyance.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***New Matter***

Claims 21-35 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 21-35 and 41 are drawn to the genus of nucleotide sequences that inhibit tumor angiogenesis. The specification supports nucleotide sequences encoding at least one anti angiogenic protein or peptide. The specification provides no written support for the broader genus of nucleotide sequences that inhibit tumor angiogenesis. This genus would include nucleic acids encoding antisense and ribozyme molecules that inhibit the expression of angiogenesis stimulating proteins and peptides, as well as nucleic acids that encode transcriptional repressors of angiogenic genes. The specification fails to describe a single example of such a nucleic acid. This disclosure is not sufficient to convey to one of skill in the art that Applicant was in possession of the claimed genus at the time of the invention. The claims should be limited to nucleotide sequences encoding at least one anti angiogenic protein or peptide.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-24, 26-31, 33-35, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mixson (EP 0 819 758 A2, published 1/21/98) in view of Lu et al (Cancer Gene Therapy, 1(4): 245-252).

Mixson teaches methods of inhibiting tumor growth in a subject bearing a tumor, which comprises intravenous or intratumoral injection of DNA encoding an anti-angiogenic peptide provided with a carrier selected from the group consisting of cationic lipids, liposomes, and cationic polymer carriers. Mixson also coadministers an expression vector for p53. See e.g. page 5, lines 24-26 and 33-38; page 15, lines 41-43; and page 17, lines 2-46.

Mixson does not teach the use of RNA.

Lu teaches direct delivery to tumors in vivo of liposome/mRNA complexes, stating that liposome/DNA expression vector complexes and liposome/mRNA complexes gave comparably transfection efficacy. See also Fig. 7 on page 251 which shows an approximate 2 fold difference in expression between DNA and RNA transfection in vivo.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute mRNA for DNA in the method of Mixson. MPEP 2144.06

indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, mRNA is recognized in the art as having comparable efficacy to DNA for in vivo delivery and expression, so it would have been obvious to substitute one for the other.

Thus the invention as a whole was prima facie obvious.

Claims 25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mixson (EP 0 819 758 A2, published 1/21/98) and Lu et al (Cancer Gene Therapy, 1(4): 245-252), as applied to claims 21-24, 26-31, 33-35, and 41 above, and further in view of Lee et al (US Patent 5,908,777, issued 6/1/99).

The teachings of Mixson and Lu are detailed above. These references do not explicitly teach a micelle carrier

Lee teaches that micelles are art-recognized equivalents of liposomes and cationic polymers. See Detailed Description paragraph 12 which states:

"The category of suitable cationic helper molecules is illustrated by (1) non-monovalent cations such as Ca.sup.2+, Mg.sup.2+, Mn.sup.2+, Al.sup.3+, and spermidine, (2) cationic polymers such as polylysine, DEAE-dextran, spermine, spermidine, protamine, polybrene, cationized proteins, cationic micelles and cationic liposomes, and (3) cationic detergents such as DC-chol, cetyltrimethylammonium bromide (CTAB), etc."

As stated above MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious.

Thus the invention as a whole was prima facie obvious.

### *Response to Arguments*

Applicant's arguments filed 10/21/04 have been fully considered but they are not persuasive.

Applicant argues that the Mixson reference relied upon in the rejections is not available as prior art because the claims have benefit of priority to the filing date of the '526 parent application, i.e. 12/5/97. This is unpersuasive for the reasons given above under "Priority", i.e. to the extent that the claims embrace methods of delivering RNA, their effective priority date is 2/10/00, the filing date of 09/500,838. This rejection could be overcome eliminating RNA from the scope of the claims. by limiting the claims to methods of delivering DNA

### *Conclusion*

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.

DAVE TRONG NGUYEN
PRIMARY EXAMINER